Customer No. 22442

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	Group Art Unit: 1644
Erwin GELFAND et al.	Examiner: Nora M. Rooney
Application No.: 10/808,846	Confirmation No.: 6711
Filed: March 24, 2004	DECLARATION OF CATHERINE LAPLACE, BSc., UNDER 37 C.F.R. § 1.132
Attorney Docket No.: 5802-1-1	
For: MODULATION OF γδ T CELLS TO REGULATE AIRWAY HYPERRESPONSIVENESS	*Submitted Via Electronic Filing*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

I, Catherine Laplace, BSc., hereby declare as follows:

1. I am currently employed by Innate Pharma, S.A. as a Research and Development Engineer and have held this position since 2000. During my work at Innate Pharma, I have subcontracted a study (with scientists of the California National Primate Research Center (CNPRC) at a UC Davis university who have developed a non-human primate model of asthma) to conduct experiments assessing the action of γδ T cells in airway illnesses.

2. It is my understanding that Innate Pharma, S.A. is a licensee of the above-identified patent application;

3. This Declaration is being submitted in conjunction with an Amendment and Response to an Office Action having a mailing date of November 21, 2007, in the above-identified application.

4. I have reviewed, and I am familiar with, the above-identified application and the presently pending claims, and I have also reviewed documents from the file history of this application, including the Office Action mailed November 21, 2007. The following discussion pertains to the Examiner's rejection of Claims 36-53 under 35 U.S.C. § 112, first paragraph, on the

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basis of enablement. In particular, the following discussion addresses the Examiner's argument that the specification does not enable the invention that is claimed.

5. It is my understanding that the Examiner's contends that the specification does not teach one skilled in the art a method for reducing airway hyperresponsiveness in a mammal by administering a phosphoantigen. The experiments set forth in the Appendices below were conducted to assess the effect of phosphoantigen treatment on early airway responses to inhaled allergen in rhesus macaque monkeys. The phosphoantigen administered is referred to as "compound X."

Appendix A describes the experimental protocol used. As described in the Examples of the above-identified application, animals were sensitized by exposure to an allergen (along with non-sensitized controls) followed by repeated aerosol challenge with the same allergen and an assessment of airway responsiveness in each animal.

Appendix B shows the airway resistance in three macaque groups: one group non-sensitized, another HDMA-sensitized and the final group HDMA-sensitized and administered compound X prior to a second HDMA challenge. All macaques were challenged twice. In the HDMA sensitized and compound X treated macaques, the first challenge occurs before the administration of compound X and the second challenge takes place when the monkey is treated by compound X.

The data presented in Appendix B demonstrate a reduction in airway hyperresponsiveness in monkeys upon administering a phosphoantigen. . As can be established from the figure in Appendix B, the phosphoantigen-treated sensitized animal (open dots) experienced a decrease of 43% in early airway response, whereas the untreated sensitized animal (solid squares) experienced a significantly lower decrease (17%). No airway response to the inhalation of allergen was observed in the non-sensitized control monkey (solid triangles). Additionally, the report handled by the subcontractor to accompany these data states: "*In monkeys treated with the phosphoantigen, there was a decrease in the early airway response. [...] While limited, the data would suggest that the phosphoantigen treatment attenuates early airway responses to inhaled allergen.*" The data therefore tend to show a reduction of AHR diseases i.e.COPD in a non-human primate model.

The complete formula of compound X is not shown due to confidentiality reasons. However, compound X is a phosphoantigen, and, as shown in Appendix C, has a structure quite similar to IPP. In particular, both compound X and IPP contain two phosphate groups positioned on the same end

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of the molecule. Likewise, compound X and IPP share a similar carbon backbone structure and are similar in molecular weight.

Appendix D describes a protocol used to assess the amount of TNFα released by γδ T cells following stimulation with a phosphoantigen. Using this protocol, γδ T cells were stimulated with one of the following phosphoantigens: compound X, IPP or BrHPP and the amount of TNFα released determined. The EC50 was then calculated for each compound. As shown in the figure of Appendix E, compound X, BrHPP and IPP are each able to stimulate γδ T cells. This stimulation of γδ T cells by compound X (or with IPP or BrHPP) results in the release of TNFα, as described in the above-referenced patent application.

6. I hereby declare that all statements made herein of my own are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the subject application or any patent issuing therefrom.

Signed: _____
Catherine Laplace, BSc.

Date: March 4th, 2008

Appendix A

The following protocol is based on Schelegle ES, Gershwin LJ, Miller LA, Fanucchi MV, Van Winkle LS, Gerriets JP, Walby WF, Omlor AM, Buckpitt AR, Tarkington BK, et al. "Allergic asthma induced in rhesus monkeys by house dust mite (*Dermatophagoides farinae*)". Am J Pathol 2001; 158:333–341.

Animal Protocol

6 male juvenile rhesus macaques (approx 2-3 years old) were kept in air filtered rooms and divided into 3 groups: non-sensitized, HDMA-sensitized and HDMA-sensitized + compound X treatment. Four monkeys were sensitized for a period of 3 months: they received three subcutaneous priming injections (2 weeks apart) of house dust mite antigen extract (HDMA) in alum. Further sensitization consisted of subcutaneous and intranasal HDMA treatments (3/week for two weeks) and a series of HDMA aerosol administrations for 6 weeks (biweekly, face mask system). Following the sensitization process, the sensitized animals received an HDMA aerosol exposure approximately twice per month. Non-sensitized animals received no HDMA injections or HDMA aerosols for the time of the sensitisation.

Airway responsiveness challenge consisted of aerosol administration of increasing repeated HDMA doses for 30 minutes. After the dust mite challenge, pulmonary mechanics were measured for 6 hours for the evaluation of responsiveness. Two challenges were performed two weeks apart: on the day of the second challenge, compound X was administered to two sensitized monkeys together with the HDMA challenge. Response analysis was assessed by calculating the percentage of airway resistance decrease at the early response point.

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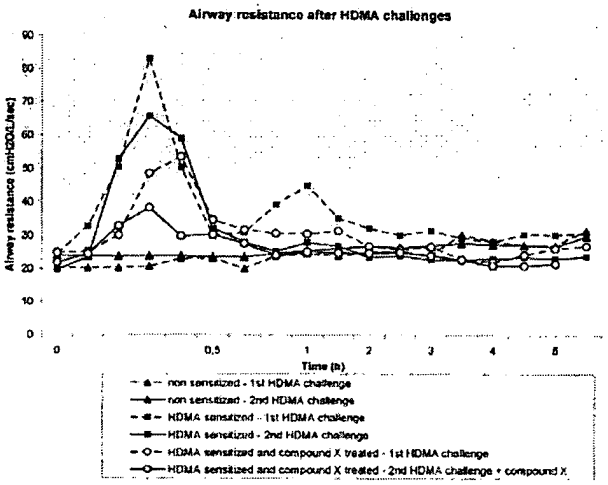
Appendix B



The above graph shows an example of the airway response developed in monkeys treated according to the experimental protocol described in Appendix A.

- ▲ Dark triangles represent non-sensitized monkeys.
- ■ Dark squares represent sensitized monkeys.
- o Open dots represent sensitized and compound X-treated monkeys.

The response after the first challenge is represented by dotted lines and the response after the second challenge (and optionally the compound X treatment) is represented by solid lines.

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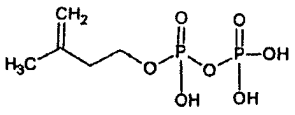
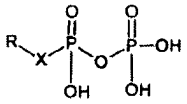
Appendix C

Structures of IPP and compound X



IPP



Compound X

X is carbon or a heteroatom, R is a substituted alkyl residue.

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Appendix D

TNFα Release Protocol

Cells (primary polyclonal human Vγ9Vδ2 T cells expanded *in vitro* and stored frozen at day 12-15 of expansion) were thawed and rinsed twice and centrifuged. Upon elimination of supernatant and resuspension of cells, the cells were incubated for 24 hours at 37°C in the presence of IL-2 (final concentration of 100 IU/ml). The cells were then washed and centrifuged, the supernatant eliminated, and the cells resuspended and adjusted to the adequate final concentration prior to being added to the wells of a 96-well plate.

To one row of wells was added a standard dilution series of (R,S)-3-(bromomethyl)-3-butanol-1-yl-diphosphate (R,S-BrHPP) and isopentenylpyrophosphate (IPP). Compound X was added to experimental wells after several dilutions.

Full plates were incubated 24 hours at 37°C for stimulation of the γδ cells with the test compound and reference compounds, BrHPP and IPP, as further described below. After this time, 100 µl of culture supernatant was taken for TNFα analysis. Measurement of the amount of released TNFα was performed as described by the manufacturer's instruction in the TNFα enzyme immunoassay kit (ref. 11121, Immunotech – Beckman Coulter). Optical Density (OD) at 405nm was read, the OD being proportional to the concentration of released TNFα in the culture supernatant. The data were processed with Excel software to compare concentration of test compound versus concentration of TNFα and for the calculation of the EC50 for each test compound.

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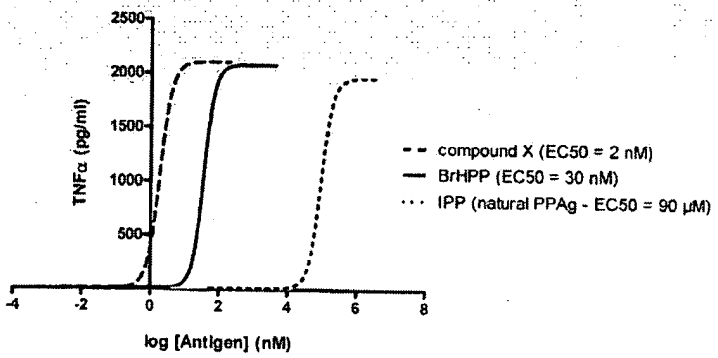
Appendix E



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